

Myeloid-derived suppressor cells in B cell malignancies

Yaghoub Yazdani¹ · Mousa Mohammadnia-Afrouzi² · Mehdi Yousefi^{3,4} ·
Enayat Anvari⁵ · Ghasem Ghalamfarsa⁶ · Hadi Hasannia⁷ · Sanam Sadreddini³ ·
Farhad Jadidi-Niaragh⁷

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Abstract Tumor cells use several mechanisms such as soluble immune modulators or suppressive immune cells to evade from anti-tumor responses. Immunomodulatory cytokines, such as transforming growth factor- β , interleukin (IL)-10, and IL-35, soluble factors, such as adenosine, immunosuppressive cells, such as regulatory T cells, NKT cells and myeloid-derived suppressor cells (MDSCs), are the main orchestra leaders involved in immune suppression in cancer by which tumor cells can freely expand without immune cell-mediated interference. Among them, MDSCs have attracted much attention as they represent a heterogeneous population derived from myeloid progenitors that are expanded in tumor condition and can also shift toward other myeloid cells, such as macrophages and dendritic cells, after tumor clearing.

MDSCs exert their immunosuppressive effects through various immune and non-immune mechanisms which make them as potent tumor-promoting cells. Although, there are several studies regarding the immunobiology of MDSCs in different solid tumors, little is known about the precise characteristics of these cells in hematological malignancies, particularly B cell malignancies. In this review, we tried to clarify the precise role of MDSCs in B cell-derived malignancies.

Keywords B cell malignancies · Lymphoma · Leukemia · Multiple myeloma · Myeloid-derived suppressor cells · Immune suppression

Introduction

Tumor cells escape from anti-tumor immune responses in part through induction of immunosuppressive microenvironment in which immune cells cannot eradicate tumor cells. Several immunosuppressive mechanisms are involved in tumor-induced suppression, including soluble factors and immunosuppressive cells. Soluble immunosuppressive factors such as transforming growth factor (TGF)- β , interleukin (IL)-10, IL-35, adenosine, and hypoxia inducible factor (HIF) can enhance tumor growth through inhibition of anti-tumor responses [1–3]. There are also various immunosuppressive cells such as regulatory T (Treg) cells [4], type II natural killer T (NKT II) [5], tumor-associated macrophages [6], and myeloid-derived suppressor cells (MDSCs) [7] that can help to tumor escape process. In the most common types of the cancers, the combination of these immunosuppressive factors contributes to inhibition of anti-tumor responses. However, MDSCs have attracted the high attention in recent years due to their complex immunobiology in various cancer and autoimmune diseases [8].

✉ Farhad Jadidi-Niaragh
f-jadidin@razi.tums.ac.ir; farhad_jadidi1986@yahoo.com

¹ Infectious Diseases Research Center and Laboratory Science Research Center, Golestan University of Medical Sciences, Gorgan, Iran

² Department of Immunology and Microbiology, School of Medicine, Babol University of Medical Sciences, Babol, Iran

³ Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

⁴ Department of Immunology, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

⁵ Department of Physiology, Faculty of Medicine, Ilam University of Medical Sciences, Ilam, Iran

⁶ Cellular and Molecular Research Center, Yasuj University of Medical Sciences, Yasuj, Iran

⁷ Department of Immunology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

MDSCs are a heterogeneous population of cells derived from myeloid progenitor cells and immature myeloid cells. MDSCs were initially identified as natural suppressor cells in tumor-bearing mice about three decades ago [9]. While the murine-derived MDSCs are characterized by the expression of Gr-1 and CD11b molecules, the human MDSCs exhibit CD33⁺HLA-DR^{low/-} phenotype. It has been shown that MDSCs exert their immunosuppressive function through various mechanisms such as the production of reactive oxygen species (ROS), nitric oxide (NO), arginase, and cytokines [10]. Several studies have investigated the role of MDSCs in different solid tumors; however, little is known regarding the immunobiology of these cells in B cell malignancies [11, 12]. Therefore, we reviewed studies related to the role of MDSCs in various B cell-derived malignancies in order to enlarge and clarify the precise function of these cells in B cell cancers.

Myeloid-derived suppressor cells

MDSCs are a heterogeneous population derived from the myeloid cell lineage. Bone marrow-derived immature myeloid cells usually differentiate into myeloid cell lineage including mature granulocytes, macrophages, or dendritic cells (DCs); however, in some pathological conditions such as cancer, a partial block of their differentiation leads to development of MDSCs. These pathologically expanded cells are not a discriminated subtype of myeloid cells but rather a complex heterogeneous population of activated immature myeloid cells that their development into mature cells is inhibited [13]. It is now evident that MDSCs are not solely the consequent of myeloid precursor cells development during long-term pathological situation. MDSC term is the functional description of immature myeloid cells that have earned various immunosuppressive properties [14].

MDSC population contains a mixture of myeloid cells with granulocytic and monocytic phenotype. MDSCs in mice are characterized by the expression of Gr1 (Ly6G) and CD11b (α M-integrin) molecules, that constitute about the 20–30 % of the normal bone marrow cells and 2–4 % of spleen cells and are absent from the lymph nodes. MDSCs in humans are usually characterized by the CD14⁺CD11b⁺ phenotype; however, they can also be defined as CD33⁺ (common myeloid marker) HLA-DR⁻ cells that do not express markers of mature myeloid and lymphoid cells. Recently, it is suggested that CD15 and CD66b molecules may discriminate granulocytic and monocytic MDSCs (G-MDSC and M-MDSC) in peripheral blood of humans [15]. In mice, a Gr-1^{high} MDSCs are mainly granulocytic; however, a Gr-1^{int} cells contain M-MDSCs [16, 17]. As anti-Gr-1 monoclonal antibody binds to two molecules belonging to the Ly6 superfamily, Ly6G and Ly6C, the use of this antibody could not precisely discriminate MDSCs subsets [18,

19]. G-MDSCs exhibit CD11b⁺Ly6G⁺Ly6C^{low} high SSC phenotype; however, M-MDSCs have CD11b⁺Ly6G⁻Ly6C^{high} low SSC morphology. M-MDSCs express higher levels of F4/80, CD115, 7/4, and CCR2 molecules compared to G-MDSCs, at least in some tumor models [20]. Discrimination of these two subsets is important as they exert different functions in pathologic conditions such as cancer. For example, it is suggested that G-MDSCs have higher capacity for expansion in animal tumor models and use different immunosuppressive mechanisms, whereas only M-MDSCs can differentiate into mature DCs and macrophages, *in vitro* [15, 21]. Other surface molecules such as CD80 (B7.1), CD115 (macrophage colony-stimulating factor receptor), and CD124 (IL-4 receptor α) have also been suggested in order to classify MDSCs to further subsets [15]. However, it is demonstrated that these markers cannot characterize specific subset of MDSCs in several tumor models [21]. As G-MDSCs exert their immunosuppressive effects mainly through ROS, it seems they use cell contact-dependent mechanisms, which implies antigen-specific interaction between MDSC and T cells [22]. On the other hand, M-MDSCs inhibit anti-tumor responses usually through NO, arginase, and cytokines which rely on cell contact-independent mechanisms and target antigen-independent T cell responses [23]. Although G-MDSCs are more prevalent in peripheral lymphoid organs in many tumor models [21], it is generally proposed that M-MDSCs exhibit higher immunosuppressive effects compared to G-MDSC in tumor microenvironment [24, 25]. This is consistent with what observed regarding the antigen-specific tolerance of T cells in peripheral lymphoid organs in most tumors and their ability to respond to non-specific stimuli [26]. However, it should be noted that the ratio of G-MDSC to M-MDSC in various experimental models can be highly variable and depends on several factors in tumor microenvironment and peripheral [25].

As the cells with the abovementioned phenotypes do not exhibit the functional characteristics of MDSCs in normal humans and mice, it seems that these cells do not really exist in healthy non-pathologic conditions, and we propose to call them as MDSC-like or non-MDSC immature myeloid cells. Thus, MDSCs develop only during time-consuming untreated pathological conditions such as chronic inflammatory infectious diseases or cancer.

It is demonstrated that several biologic factors affect the development, expansion, and activation of MDSCs, such as cytokines, toll-like receptor ligands, and complement proteins. These factors are mainly supplied by T cells, tumor cells, and tumor stroma. These factors altogether enhance the signaling pathways that induce the set of MDSC-promoting transcription factors including signal transducer and activator of transcription (STAT)3, STAT1, STAT6, and nuclear factor (NF)- κ B [27].

Several factors such as cyclooxygenase-2 (COX2), prostaglandins, macrophage colony-stimulating factor (M-CSF),

granulocyte/macrophage colony-stimulating factor (GM-CSF), G-CSF, vascular endothelial growth factor (VEGF), and interferon (IFN)- γ can affect the expansion and function of MDSCs [28].

Activation of COX pathway in tumor cells leads to upregulation of PGE2 which is involved in inflammatory processes and supports tumorigenesis. PGE2 can also recruit MDSCs into tumor region and promote myeloid cell differentiation toward MDSC, which then enhances tumor growth [29]. Ligation of PGE2 receptor E-prostanoid (EP) 4 in MDSCs could upregulate arginase 1 expression [30]. Furthermore, stimulation of EP receptor agonists with PGE2 promoted the generation of MDSC from bone marrow stem cells [31]. There is evidence which implies that PGE2 affects the expression of arginase 1 and NOS2 [32].

It is demonstrated that high levels of M-CSF inhibit the proper myeloid development, leading to expansion of MDSCs. Moreover, upregulation of M-CSF in pathological conditions was associated with expansion of MDSCs [33]. Migration of macrophages to inflammatory tissues was also associated with increased levels of M-CSF that contributes to expansion of MDSCs [34]. However, it is a matter of debate that whether MDSCs express M-CSF receptor or not. Administration of anti-M-CSF receptor monoclonal antibody to mice prevented the infiltration of M-MDSCs in lung and prostate tumors [35].

GM-CSF promotes antigen presentation by DCs and increases T cell responses at low concentrations [36]. In contrast, high concentration of GM-CSF is associated with downregulation of DC differentiation and expansion of CD11b⁺Gr-1⁺ MDSCs [37]. Cancer cells can produce GM-CSF that enhances the induction and expansion of MDSCs in secondary lymphoid organs and at the tumor region [38]. Treatment of mice with recombinant GM-CSF substantiated the stimulatory effect of this factor on MDSCs [39]. Concentration of GM-CSF and length of stimulation are two important factors that assign the immune stimulatory or immune suppressive effects of this factor on immune responses. GM-CSF may also affect differentially on development of various MDSC subsets. While it induces both CD11b⁺Gr-1^{int} and CD11b⁺Gr-1^{low} subtypes in the spleen of tumor-bearing mice, it enhanced only the CD11b subset in the bone marrow [24].

G-CSF promotes the expansion of MDSCs in tumor models, which is in part through the upregulation of various cytokines and transcription factors that enhance MDSC expansion [40]. It has also been demonstrated that MDSC-inducing cytokines such as IL-1 and IL-17 can also stimulate G-CSF generation [41, 42]. Moreover, upregulation of G-CSF responsive genes, including PU.1 and C/EBP β , was associated with MDSC expansion [43, 44]. Furthermore, signaling of G-CSFR leads to activation of STAT3 [45] which is the main MDSC-inducing transcription factor [46]. There is also evidence which implies

the stimulatory effect of G-CSF on the expansion of G-MDSCs in tumor models [47]. There are also other studies that show MDSCs can upregulate MDSC-inducing signaling pathways such as Jak/Stat pathway [48]. Thus, it seems that the high concentrations of G-CSF can expand MDSCs.

Ligation of VEGFR1 improves the generation of Gr-1⁺ myeloid cells [49]. Signaling of VEGFR2 also induces CD11b⁺Gr-1⁺ MDSCs accompanied with the expansion of B cells at the pro-B cell stage [50]. Continuous signaling through VEGF inhibits NF- κ B and FLT3L signals which lead to expansion of immature myeloid cells [51]. Stimulation of MDSCs by exogenous or autocrine IFN- γ also leads to upregulation of arginase1, inducible nitric oxide synthase (iNOS), and IL-13 in these cells, and induces the expression of IL-4 and IL-13 receptors [16]. While the blockade of IFN- γ secretion inhibited MDSC-induced T cell suppression [16], the synergistic function of IFN- γ produced by T cells and MDSCs increases the immunosuppressive effect of MDSCs in both STAT1-dependent and STAT1-independent manners [52]. It is suggested that IFN- γ promotes the generation of MDSCs in part through the activation of interferon regulatory factor-8 (IRF-8) [53].

To lesser extent compared to the abovementioned factors, other biologic materials, such as TGF- β , stem cell factor (SCF), IL-1 β , IL-6, IL-4, IL-10, IL-12, IL-13, and matrix metalloprotease-9 (MMP-9), can also affect the expansion and function of MDSCs [54].

Most of the abovementioned factors use Janus kinase (JAK) and STAT signaling molecules that mainly contribute to cell survival, proliferation, differentiation, and apoptosis. Among the STAT molecules, STAT3 exerts the highest effect on the induction, expansion, activation, and suppressive function of MDSCs. Tumor-derived factors can activate JAK2 and STAT3 signaling molecules which were associated with expansion of MDSCs, *in vitro* [55]. STAT3 was also upregulated in MDSCs isolated from tumor-bearing mice [56]. Inhibition of STAT3 also led to downregulation of MDSCs which was associated with augmented T cell responses in mice tumor models [57]. It is suggested that STAT3 promotes the development of MDSCs in part through some downstream molecules such as calcium-binding pro-inflammatory proteins S100A9 and S100A8 [58], and Nox2 transcription factor [59] which prevent DC differentiation and enhance MDSC expansion and activation [60]. STAT3 can also affect the development and function of MDSCs by downregulation of protein kinase (PK) C β II [61], upregulation of CCAAT-enhancer-binding protein beta (C/EBP β) [62], and modulation of acute-phase proteins [63]. Thus, it seems that continuous activation of STAT3 in myeloid progenitors under pathological condition leads to induction and expansion of MDSCs.

STAT1 is another effective signaling molecule in the activation and suppressive function of MDSCs. IFN- γ and IL-1 β

can activate STAT1, which then induces iNOS and arginase enzymes in MDSCs [64]. It is suggested that STAT1 signaling has higher effects on the function of M-MDSCs compared to G-MDSCs [52]. Moreover, STAT5 can also modulate the survival of MDSCs. This claim was resulted from the study of the effect of sunitinib on the survival of MDSCs isolated from spleen and tumor of mice and humans [65].

Ligation of CD124 (IL-4R α) on the MDSCs with IL-4 or IL-13 leads to activation of STAT6 signaling, which then activates arginase [66] and upregulates TGF- β generation [67]. There is another evidence which implies the role of STAT6 signaling in the accumulation of MDSCs [68]. There is also a synergism between STAT1 (induced by IFN- γ) and STAT6 (induced by ligation of CD124) signaling pathways for promotion of MDSC suppressive functions [16].

Activation of NF- κ B transcription factor following exposure to infectious microorganisms can expand MDSCs [69]. Ligation of TLRs or signaling of IL-1 or IL-18 cytokines trigger NF- κ B signaling in Myd88-dependent manner. Accordingly, treatment of mice with IL-1 receptor antagonist prevented gastric cancer which was associated with downregulation of MDSCs [70]. Moreover, administration of tumor exosomes to mice led to increased tumor metastasis in the lung accompanied with MDSC accumulation [71]. Thus, it seems that microbial-associated cancers may enhance recruitment and expansion of MDSCs in part through the activation of NF- κ B signaling by TLR ligands or IL-1 and IL-18 cytokines.

In spite of controversial reports, it seems that Notch signaling pathway can also promote the induction and expansion of MDSCs [72]. There are also other signaling pathways such as Ras, PI3K, and TGF- β that can affect the development of MDSCs [27, 73].

MDSC can promote tumor growth by enhancing angiogenesis and suppression of anti-tumor responses. These cells stimulate angiogenesis process in part through the secretion of MMP and VEGF factors [74]. MDSCs can affect on both the innate and adaptive immune responses; however, their role in the suppression of T cell responses is better understood compared to other cells. Among the innate immune cells, MDSCs suppress NK cell cytotoxicity, promote the differentiation of M2 macrophages, and confine the priming capacity of mature DCs [75].

MDSCs suppress T cell responses through both contact-dependent or contact-independent and antigen-specific or non-specific mechanisms. There are various suppressive mechanisms, including induction of apoptosis [76], secretion of immunomodulatory factors (e.g., H₂O₂, TNF- α , NO, TGF- β) [77, 78], modulation of amino acid (tryptophan, arginine, and cysteine) metabolism [79], induction of Treg cells [80], and restriction of T cell homing [81], by which MDSCs exert their immunosuppressive function (Fig. 1).

MDSCs hydrolyze L-arginine to urea and L-ornithine by arginase enzymes (ARG1 and ARG2) and the iNOS2. L-ornithine is one of the main factors for the generation of cell cycle-promoting polyamines that enhances the proliferation of tumor cells [82]. Accordingly, there are several studies that imply the upregulation of arginase function in various cancers [83, 84]. Catabolism of L-arginine by MDSCs leads to decreased availability of this cytokine from the microenvironment, which then results in decreased proliferation and cytokine production by T cells [85]. The lack of L-arginine affects T cells in part through downregulation of CD3 ζ chain [86] and cyclin D3 and cyclin-dependent kinase 4 (CDK4) that are the cell cycle regulators [87]. Moreover, NO exerts its immunosuppressive function through mechanisms such as the prevention of JAK3 and STAT5 and induction of apoptosis [88] in T cells, and downregulation of MHC class II [89]. Competition for cysteine is another way by which MDSCs suppress T cell activation [79]. As T cells have none of the cysteine supplying tools including cystathionase (for conversion of methionine to cysteine) or the xCT chain of the xc-transporter (for importing cysteine) [90, 91], so they cannot provide cystine for themselves, leading to complete dependence to use of ASC neutral amino acid plasma membrane transporter. On the other hand, although MDSCs can import cystine, however, they cannot convert it to methionine or cysteine because they lack cystathionase. Similarly, MDSCs lack ASC neutral amino acid transporter, so they only import cystine without exporting cysteine, which leads to competition for cysteine [79]. Thus, MDSCs sequester cystine and deprive T cells from cysteine. It has also been shown that MDSCs express the tryptophan-degrading enzyme indoleamine 2,3-dioxygenase (IDO) which can inhibit anti-tumor responses and help to tumor growth [80].

Production of reactive oxygen and nitrogen species is another mechanism through which MDSCs inhibit anti-tumor responses. Several studies have been reported that the generation of ROS significantly increased by MDSCs in various cancers [92]. Production of ROS is one of the main immunosuppressive mechanisms of MDSCs, as demonstrated blocking ROS generation leads to defective suppressive action of MDSCs in mice and humans, *in vitro* [93].

Arginase and iNOS are concomitantly modulated by Th1 and Th2 cytokines and can synergistically suppress antigen-specific T cell responses. Synergistic function of these enzymes leads to generation of reactive nitrogen oxide species (peroxynitrites) by NOS2 under limited L-arginine availability situation [94], which induces apoptosis in antigen-specific T cells via inhibition of tyrosine phosphorylation of essential proteins required for T cell activation such as TCR and CD8 [95]. Interestingly, this function of MDSCs through peroxynitrites affects only TCR-expressing T cells which contact with the peptide presented

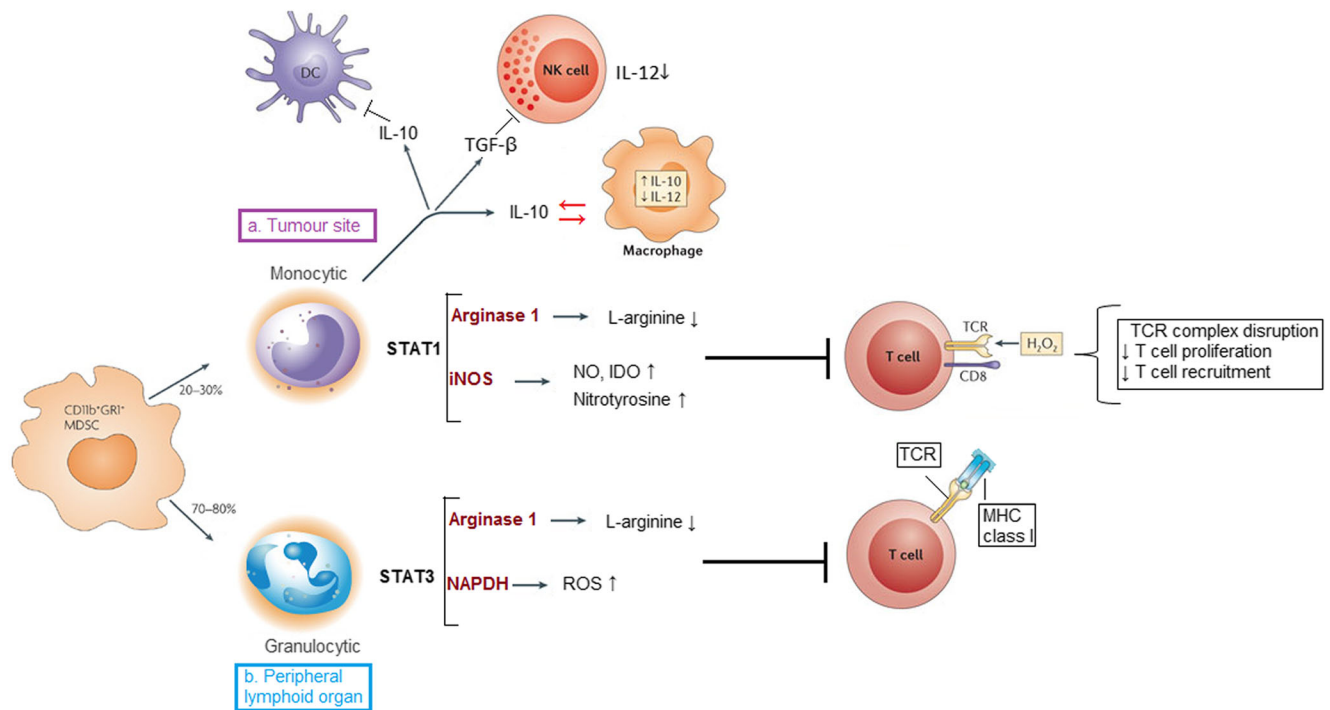


Fig. 1 MDSCs exert their immunosuppressive functions through various mechanisms such as secretion of immunomodulatory factors (e.g., H_2O_2 , $TNF-\alpha$, NO, $TGF-\beta$), modulation of amino acids metabolism, induction of Treg cells, and restriction of T cell homing. In the tumor region, M-MDSCs are dominant subset of MDSCs which provide immunosuppressive microenvironment for malignant cells, whereas G-MDSCs are the main subset of MDSCs in peripheral. MDSCs inhibit

macrophages, DCs, and NK cells through cytokines such as IL-10 and $TGF-\beta$. On the other hand, they suppress T cells by arginase and iNOS mechanisms. DCs dendritic cells, NK natural killer cells, *STAT* signal transducer and activator of transcription, MDSC Myeloid-derived suppressor cell, *iNOS* inducible nitric oxide synthase, NO nitric oxide, IDO indoleamine-2,3-dioxygenase, ROS reactive oxygen species, TCR T cell receptor, IL interleukin

by MDSCs. MDSC-derived peroxynitrites disrupt the conformational structure of TCR-CD3 complex which leads to defected T cell response to antigen stimulation [96].

It has also been shown that MDSCs can promote the differentiation and expansion of Treg cells through different mechanisms such as production of Treg-promoting cytokines or antigen presentation and cell contact-dependent mechanisms [80]. In contrast, it is reported that MDSCs inhibit the generation of Treg cells by repressing $TGF\beta 1$ [97].

MDSCs may deprive naïve T cells from tumor antigens through inhibition of their homing into lymph nodes. It is suggested that MDSCs prevent the migration of T cells into lymph nodes in part through the downregulation of L-selectin on their surface [81].

The fate of MDSCs after tumor eradication is another interesting field in which there are several unanswered questions. As MDSCs can differentiate to macrophages or DCs in some culture conditions [98] and MDSCs disappear following tumor eradication by surgery [15], it is suggested that MDSCs shift toward some myeloid cells following tumor elimination which may be in part due to modification of tumor immunosuppressive microenvironment to normal circumstance. However, this field deserves further investigations as

it may also be possible that MDSCs fall into apoptosis process after their growth factors starvation.

MDSCs in B cell malignancies

Multiple myeloma

Multiple myeloma (MM) is a B cell-derived malignancy which is characterized by the expansion of proliferating plasma cells within the bone marrow (BM) and the accumulation of monoclonal antibodies in the peripheral blood [99].

5T2 and 5T33MM derived from elderly C57BL/KaLwRij mice are two most prevalent mouse models for in vivo study of MM [100]. Using these animal models, Van Valckenborgh and colleagues have shown that there is a significant shift toward M-MDSCs ($CD11b^+Ly6G^{low}$) in the BM of 5T2 and 5T33MM mice at the end stage of the disease. M-MDSCs could also be subdivided to various subsets based on Ly6C expression including inflammatory monocytes ($Ly6C^{high}SSC^{low}$), eosinophils ($Ly6C^{int}SSC^{high}$), and immature myeloid cells ($Ly6C^{int}SSC^{low}$). Among them, inflammatory monocytes exert the highest immunosuppression. They

demonstrated that the frequency of immature myeloid cells is markedly increased in the BM of MM mice models, which implies a differentiation block in the development of myeloid cells. Moreover, M-MDSCs had higher capacity for suppression of T cells compared to G-MDSCs. Myeloma-derived MDSCs also expressed higher levels of inhibitory molecules such as iNOS, arginase-1, and IL-10, compared to naïve mice MDSCs. They suggested that MDSCs exert their immunosuppressive function in part through iNOS, as inhibition of iNOS by L-NMMA led to attenuation of MDSC inhibitory effects on T cell proliferation [101]. Using 5TGM1 model, it has been shown that MDSCs accumulate in the blood, BM, and spleen over time following 5TGM1-GFP myeloma cells inoculation. Moreover, these tumor-induced MDSCs could differentiate into mature and functional osteoclasts both in vitro and in vivo which then led to bone destruction. Interestingly, MDSCs derived from myeloma-bearing mice differentiate to osteoclasts with significantly higher capacity compared to normal mice-derived MDSCs, both in vitro and in vivo [102]. It should be noted that osteoclasts enhance cancer-associated osteolytic lesions in MM. Using an immunocompetent mouse model of breast cancer bone metastasis, Sawant and colleagues demonstrated that only tumor-derived MDSCs can differentiate to osteoclasts and MDSC derived from other organs such as blood, spleen, lymph nodes, and lung are not involved in osteoclastogenesis process, both in vitro and in vivo. Moreover, this process was not observed in MDSCs derived from control or tumor-bearing mice without bone metastasis, implying the critical role of BM-derived factors for differentiation of MDSCs to osteoclast [102]. In another study, Ramachandran et al. reported that CD11b⁺CD14⁺CD33⁺ immunosuppressive MDSCs are significantly increased in BM of newly diagnosed MM patients. Moreover, they investigated the role of MDSCs in mice injected with intravenous tumor cell lines derived from transgenic Bcl-xl/Myc mice (ATLN and DP42). Their results showed that both M-MDSC and G-MDSC populations were increased in mice as early as 1 week after MM cell inoculation. Investigation of MDSCs in S100A9 deficient MM inoculated mice showed the decreased frequency of these cells in the BM which was associated with upregulation of antigen-specific CD8⁺ T cells in BM and spleens and was abrogated by the administration of anti-CD8 antibody or adoptive transfer of MDSC. Moreover, MDSCs from MM-bearing mice exerted significantly higher immunosuppressive effect compared to immature myeloid cells from naïve mice. Authors suggested that expansion of MDSCs at early stages of MM plays a key role in disease progression [103]. It is observed that the frequency of MDSCs in the BM initially increases, however, then gradually reduces at the end stages of disease, as observed in the MM mice models [11]. There is other evidence which more substantiates this claim. De Veirman et al. reported that MDSCs accumulate in the BM of 5TMM mice during MM progression in early

stages of disease, while they were increased in circulation at later stages. Moreover, in vivo depletion of MDSCs via anti-GR1 antibodies and 5-fluorouracil led to tumor attenuation in 5TMM mice [104]. It seems that cell to cell communications between malignant cells and myeloid progenitor cells may lead to initial upregulation of MDSCs in the BM. It is suggested that MM cells induce MDSCs and enhance their survival in part through secretion of soluble factors that increase the expression of Mcl-1 in MDSCs [104].

It is reported that the frequency of CD14⁺ HLA-DR^{low} M-MDSCs is increased in the peripheral blood of patients with MM at diagnosis stage [105]. On the other hand, there is evidence which indicates the intact frequency of M-MDSC and increased CD11b⁺CD14⁺CD33⁺CD15⁺ [103] or CD11b⁺CD14⁺CD33⁺CD15⁺HLA-DR^{low} [106] G-MDSCs in the BM and peripheral blood of MM patients. There are similar results regarding the increased frequency of G-MDSCs in the peripheral blood of MM patients with progressive disease [107]. Franssen et al. have also been reported that the frequencies of highly suppressive CD14⁺ MDSCs, CD14⁺ MDSCs, and Treg cells are increased in the blood of MM patients [108]. These discrepancies may be in part due to various sample sizes and different therapeutic drugs of MM patients. It should be noted that both M-MDSC and G-MDSC isolated from BM of MM patients could inhibit T cells in vitro, while immature myeloid cells of normal individuals had not immunosuppressive properties [103]. Although it is reported that MDSCs help the growth of MM cells in part through suppression of T cells [106], little is known regarding the mechanisms by which MDSCs accumulate in MM patients. It is suggested that MM cells or other BM-derived stromal cells may secrete various MDSC-promoting factors such as IL-6, GM-CSF, VEGF, and IL-1 β , which help to development of MDSCs [109, 110]. These cytokines are also involved in several adaptive and innate immune responses [111–113].

It is recently demonstrated that G-MDSCs can significantly suppress both CD8⁺ T and NKT cells which was associated with MM growth. Moreover, MM cells could induce MDSCs from peripheral blood mononuclear cells of normal subjects, implying a reciprocal interaction between MDSCs, MM cells, and immune effector cells. Furthermore, inhibition of MDSCs using lenalidomide and bortezomib immunomodulatory drugs led to disease attenuation in MM patients [106]. De Keersmaecker and coworkers have recently reported that CD14⁺HLA-DR^{low} M-MDSCs constitute about 3.5 % of PBMCs in MM patients. Surprisingly, they showed that both the CD11b⁺CD14⁺HLA-DR^{low} and CD11b⁺CD14⁺HLA-DR^{high} cells can exert immunosuppressive effects leading to decreased T cell proliferation and cytokine production, in vitro [114]. A latter subpopulation was expected to act as antigen presenting cell, thereby activating T cells similar to previous report; however, it is not clear how these HLA-DR^{high} cells suppressed T cells. Like the previous report, addition of

immunomodulatory drugs to in vitro coculture of MDSC/T cells led to decreased T cell proliferation, but did not affect cytokine production [114]. Other investigators reported that G-MDSCs are increased in the blood of progressive MM patients and can induce Treg cells, in vitro. They showed that both normal- and MM patients-derived MDSCs can inhibit T cell proliferation in a dose-dependent manner. Moreover, administration of G-CSF to MM patients led to increased frequency of MDSCs in the peripheral blood [107]. It is reported that administration of lenalidomide to MM patients increases the frequency of both T cells and MDSCs. Moreover, CD14⁺CD15⁺ MDSCs could suppress the proliferation of both CD4⁺ and CD8⁺ T cells, in vitro. There was a significant correlation between the frequencies of T cells, Treg, and MDSCs in lenalidomide-treated patients, which implies that lenalidomide enhances both the activating and inhibitory components of the immune system [115]. Tadalafil, a phosphodiesterase 5 (PDE5) inhibitor, is another MDSC-targeting drug which its administration to end-stage relapsed/refractory MM patients decreased MDSC function and enhanced durable anti-myeloma immune response [116]. Wang and colleagues have also been reported that the frequency of M-MDSCs is increased and correlated with disease progression in newly diagnosed and relapsed MM patients compared to MM patients in remission and normal subjects. Moreover, patient-derived plasma or MM cells could induce M-MDSCs, in vitro. Treatment of MM patients with bortezomib (proteasome inhibitor) was associated with downregulation of MDSCs [117]. Furthermore, it has recently demonstrated that the expression of PD-L1 on MDSCs is higher than antigen-presenting cells in MM patients. Moreover, blockade of PD1/PD-L1 pathway prevented MDSC-induced MM cell growth. Combination of lenalidomide and PD1/PD-L1-blockade led to further abrogation of MDSC-mediated immune suppression [118].

It seems that the frequency of MDSCs is increased in MM patients and correlates with disease progression (Table 1). Moreover, it is demonstrated that MDSCs initially expand in BM and can even differentiate to osteoclasts that induce bone lesions. Subsequently, MDSCs migrate to peripheral organs and induce systemic immunosuppression which leads to the faster disease progression.

Lymphoma

The B cell lymphomas affect B cells in the lymph nodes and usually involve older adults and immunocompromised individuals. B cell lymphomas include Hodgkin's and rarer non-Hodgkins lymphomas that can appear in low (non-progressive) and high (progressive) grades [119].

There is no comprehensive data regarding the immunobiology of MDSCs in the B cell lymphomas. It is reported that coculture of monocytes with peripheral blood

mononuclear cells (PBMCs) from 40 patients with B cell non-Hodgkin lymphoma (NHL) led to decreased proliferation of T lymphocytes, which was restored following monocyte depletion implying the suppressive effect of M-MDSCs. Although the frequency of monocytes in NHL patients was intact; however, the expression of HLA-DR on their monocytes was significantly less than normal subjects, which was associated with immunosuppressive function and disease progression indicating the increased MDSCs in NHL patients. Moreover, it is suggested that this immunosuppression is in part through arginase-1 mechanism [120].

There is evidence regarding the increased frequency of circulating monocytes and MDSCs in patients with diffuse large B cell lymphoma (DLBCL) [121, 122], follicular lymphoma (FL) [120, 123], and Hodgkin lymphoma (HL) [124] indicating the prognostic potential of these cells in B cell lymphomas [125]. In a study of 99 [121] and 366 [122] treated DLBCL patients, it is found that the absolute number of monocytes is increased and can be considered as potent prognostic marker. Moreover, investigation of lymphocyte/monocyte ratio in 103 HL patients for about 8.9 years showed that this ratio can be an independent factor for predicting clinical outcomes in HL [124]. Investigation of 99 [126] and 50 [127] FL patients showed that lymphoma-associated macrophages can be considered as worthy prognostic biomarkers for prediction of survival in FL. Similarly, another study on 194 FL patients demonstrated that low CD68 expressing intratumoral macrophages predict outcome of FL patients [128]. In another study, absolute number of monocytes at diagnosis time was associated with overall survival in 355 FL patients [122]. Increased number of CD68⁺ macrophages in nodal biopsies of 71 NHL patients has been also observed which was associated with disease progression [129].

Increased recruitment of CD68⁺VEGFR-1⁺ macrophages into perivascular regions of neovessels as well as the stromal compartment was also correlated with aggressive disease in 42 patients with NHL [130]. The frequency of myeloid progenitor cells was also correlated with disease progression in B cell lymphomas [131]. As discussed above, it seems that the frequencies of myeloid progenitors and monocytes may be considered as potent prognostic factor for B cell lymphomas. As investigated, monocytes could contain M-MDSCs and myeloid progenitors might differentiate to MDSCs; we may conclude that these studies reflect the function of MDSCs in lymphoma patients. However, it should be noted that MDSCs constitute a small fraction of monocytes or myeloid progenitors, so a direct conclusion from monocytes or myeloid progenitors to MDSCs may not be rational. Thus, we need to discuss in this field using the literatures that have directly investigated MDSCs in B cell lymphomas.

Serafini and colleagues have demonstrated that MDSCs act as tolerogenic antigen-presenting cells (APCs) which present tumor-derived antigens to Treg cells and expand these cells in

Table 1 Studies related to the role of MDSCs in multiple myeloma

Main claim	Ref.
1. The frequencies of immature myeloid cells and M-MDSCs are significantly increased in the BM of MM mice	[101]
2. M-MDSCs subdivide into various subsets based on Ly6C expression	
1. MDSCs accumulate in the blood, BM, and spleen over time in the MM mice	[102]
2. The tumor-induced MDSCs can differentiate into mature and functional osteoclasts	
1. MDSCs are significantly increased in the BM of newly diagnosed MM patients	[103]
2. Both M-MDSCs and G-MDSCs are increased in mice as early as 1 week after MM cell inoculation	
The frequency of MDSCs in the BM of MM mice initially increases, however, then gradually reduces at end stages of disease	[11, 104]
M-MDSCs are increased in the peripheral blood of patients with MM at diagnosis stage	[105]
The frequency of M-MDSCs is intact, while G-MDSCs are increased in the BM and peripheral blood of MM patients	[103]
The frequency of G-MDSCs is increased in the BM and peripheral blood of MM patients	[106, 107]
The frequencies of highly suppressive CD14 ⁺ MDSCs, CD14 ⁺ MDSCs are increased in the blood of MM patients	[108]
1. G-MDSCs suppress both CD8 ⁺ T and NKT cells which is associated with MM growth	[106]
2. MM cells induce MDSCs from peripheral blood mononuclear cells of normal subjects	
1. M-MDSCs constitute about 3.5 % of PBMCs in MM patients	[114]
2. Both CD11b ⁺ CD14 ⁺ HLADR ^{low/-} cells and CD11b ⁺ CD14 ⁺ HLA-DR ^{high} cells can exert immunosuppressive effects	
G-MDSCs are increased in blood of progressive MM patients and can induce Treg cells	[107]
Administration of lenalidomide to MM patients increases the frequency of MDSCs	[115]
Administration of tadalafil to end-stage relapsed/refractory MM patients decreased MDSC function and enhanced durable anti-myeloma immune response	[116]
1. The frequency of M-MDSCs is increased and correlated with disease progression in newly diagnosed and relapsed MM patients	[117]
2. Treatment of MM patients with bortezomib (proteasome inhibitory) was associated with downregulation of MDSCs	
1. Expression of PD-L1 on MDSCs is higher than antigen presenting cells in MM patients and its blockade prevented MDSC-induced MM cell growth	[118]
2. Combination of lenalidomide and PD1/PD-L1-blockade led to further abrogation of MDSC-mediated immune suppression	

MDSC myeloid-derived suppressor cell, MM multiple myeloma, BM bone marrow, NKT natural killer T, HLA human leukocyte antigen, Treg regulatory T cell, PD-L programmed death ligand

part through arginase but not TGF- β in A20 B cell lymphoma model. They also showed that upregulation of IL-4R α on MDSCs was associated with suppression of CD8⁺ but not CD4⁺ T cells. NOHA (arginase inhibitor) or sildenafil could inhibit Treg proliferation and tumor-induced tolerance in antigen-specific T cells through suppression of MDSCs both in vitro and in vivo [132]. Study of 91 untreated patients with DLBL showed a monocytosis in 17.6 % of the patient, which was known as an independent prognostic factor and correlated with worse overall survival. They also investigated the frequency of M-MDSCs in peripheral blood of 23 patients and reported that these cells are significantly increased in these patients compared to normal subjects [133]. This report may explain the relation between monocytosis and poor prognosis in B cell malignancies because it seems that monocytosis is usually associated with expansion of M-MDSCs.

It has been shown that CD11b⁺Gr1⁺ MDSCs persisted within lymphoid organs after treatment with cyclophosphamide and rituximab/CpG in murine B cell lymphoma expressing human CD20 [134]. Gustafson and coworkers have also been shown that while there is a positive correlation between the number of granulocytes and immunosuppressive CD14⁺HLA-DR^{low/-} monocytes, no correlation exists between CD14⁺HLA-DR^{low/-} monocytes and Lin⁻CD33⁺HLA-DR⁻ MDSCs [135]. It is also demonstrated that the ameliorative effect of lenalidomide and fusion DNA lymphoma vaccine in pre-established syngeneic

A20 lymphomas is associated with downregulation of circulating Treg and MDSCs in tumor-bearing but not naïve mice [136]. Furthermore, all circulating MDSC subsets including monocytic, granulocytic, and CD34⁺ population were increased in 60 consecutive newly diagnosed HL patients and correlated with clinical variables at diagnosis and outcome. Although all MDSC subsets were increased in HL patients, a potent prognostic significance was confined to immature CD34⁺ MDSCs [137].

Most recently, Sato et al. demonstrated that MDSCs are increased in NHL patients and inversely correlated with NK cells. Using EL4 murine lymphoma model, they showed that the Gr1⁺CD11b⁺Ly6G^{med}Ly6C^{med} MDSCs (non-monocytic and non-granulocytic) MDSCs are increased following NK cell depletion, indicating the regulatory effect of NK cells on MDSCs. It should be noted that these MDSCs secrete IL-10 but not NO or arginase. They also showed that the increased frequencies of both IL-10-producing CD14⁺HLA-DR⁻ and CD14⁻HLA-DR⁻ MDSCs in NHL patients were associated with decreased NK cells in peripheral blood [138].

As discussed above, it seems that the frequencies of myeloid progenitors, immature myeloid cells, monocytes, and MDSCs are increased in various B cell lymphomas and correlate with disease prognosis (Table 2). Moreover, administration of various therapeutic drugs was associated with downregulation of MDSCs implying the lymphoma-promoting function of these cells.

Table 2 Studies related to the role of MDSCs in B cell-derived lymphomas and leukemia

Main claim	Ref.
MDSCs induce Treg cells and expand these cells in A20 B cell lymphoma model	[132]
M-MDSCs are significantly increased in the patients with DLBCL compared to normal subjects	[133]
MDSCs persisted within lymphoid organs after treatment with cyclophosphamide and rituximab/CpG in murine B cell lymphoma expressing human CD20	[134]
While there is a positive correlation between the number of granulocytes and immunosuppressive M-MDSCs, no correlation exists between M-MDSCs and Lin [−] CD33 ⁺ HLA-DR [−] MDSCs	[135]
Lenalidomide and fusion DNA lymphoma vaccine attenuate pre-established syngeneic A20 lymphomas in pat through downregulation of circulating Treg and MDSCs	[136]
All circulating MDSC subsets including monocytic, granulocytic, and CD34 ⁺ population are increased in newly diagnosed HL patients	[137]
MDSCs are increased in NHL patients and inversely correlated with NK cells	[138]
1. The frequency of MDSCs is increased in untreated CLL patients	[80]
2. MDSCs suppress T cell activation and induce Treg cells	
3. CLL cells induce IDO ^{high} MDSCs from monocytes derived from healthy subjects	
The frequency of M-MDSCs is increased in CLL patients, which was correlated with disease progression	[139]

MDSC myeloid-derived suppressor cell, DLBCL diffuse large B cell lymphoma, HLA human leukocyte antigen, Treg regulatory T cell, HL Hodgkin lymphoma, NHL non-Hodgkin lymphoma, NK natural killer, CLL chronic lymphocytic leukemia, IDO indoleamine 2,3-dioxygenase

Leukemia

B cell-derived Leukemia is a group of B cell cancers that usually begins in the BM and leads to expansion of abnormal

B cells, which are not fully developed and are characterized as blasts or leukemia cells. Unfortunately, little is known regarding the immunobiology of MDSCs in patients with B cell leukemia. Recently, Jitschin et al. reported that the frequency

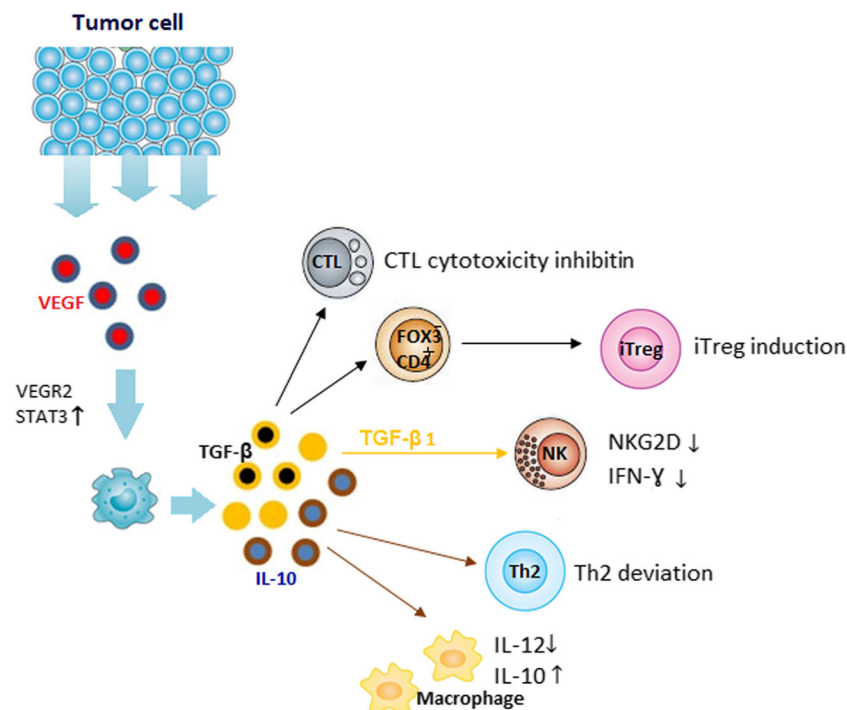


Fig. 2 Malignant B cells produce soluble factors that improve the development and activation of MDSCs. On the other hand, MDSCs induce immunosuppressive microenvironment in which malignant cells can freely expand. MDSCs can induce Treg cells through secretion of cytokines such as IL-10 and TGF-β. Moreover, MDSCs promote the differentiation of Th2 and anti-inflammatory (M2) macrophages through IL-10. Treg, Th2, and M2 macrophages supply immunosuppressive microenvironment, which help to expansion of

malignant cells. On the other hand, MDSCs directly inhibit anti-tumor responses exerted by CTLs, NK, and Th cells via inhibitory cytokines, arginase, and iNOS. VEGF vascular endothelial growth factor, STAT signal transducer and activator of transcription, MDSC myeloid-derived suppressor cell, TGF-β1 transforming growth factor beta, CTL cytotoxic T lymphocytes, FOX3 forkhead box 3, IL interleukin, CD4 cluster of differentiation, Tregs regulatory T cells, NK natural killer cells, NKG2D natural killer group 2D, IFN-γ interferon gamma, Th2 T helper 2

of CD14⁺HLA-DR^{low} MDSCs is increased in untreated CLL patients compared to normal subjects. They showed that MDSCs could suppress T cell activation and induce Treg cells, in vitro, which was in part through overexpression of IDO. Interestingly, CLL cells could induce IDO^{high} MDSCs from monocytes derived from healthy subjects, in vitro [80]. Another group has recently reported that the frequency of CD14⁺HLA-DR^{low/-} MDSCs is increased in 49 CLL patients, which was associated with disease progression and poor prognosis [139]. Thus, it seems that MDSCs are increased in B cell leukemia patients and their frequency is in correlation with MDSCs which may be in part due to stimulatory effects of leukemic B cells on expansion of MDSCs (Table 2). However, we need further investigations to know how leukemic cells induce MDSCs.

Impact of MDSCs on the molecular mechanisms responsible for B cell malignancies

Little is known regarding the B cell molecular mechanisms affected by MDSCs during tumorigenesis process. B cells in different malignancies are in different maturation stages implying the regulatory mechanism(s) which led to maturation stop and malignancy. Using cocultures of BM-derived cells with OP9 stromal cells, Kennedy and colleagues have recently reported that adipocyte-conditioned medium enhances the generation of CD11b⁺Gr1⁺ MDSCs, which can block B cell development, in vitro. As addition of anti-IL-1 antibodies restored B lymphopoiesis, they implied that MDSCs exert their inhibitory effect in part through secretion of IL-1 cytokine. Moreover, they demonstrated that arginase and iNOS enzymes did not affect B cell lymphopoiesis process [140]. Another study has indicated that mouse M-MDSCs inhibit B cell responses against LP-BM5 retrovirus infection through iNOS/NO and the MDSC-expressed negative-checkpoint regulator VISTA. It should be noted that they did not investigate the role of arginase or soluble factors in inhibition of B cell responses [141]. Other investigators showed that M-MDSCs from CIA mice inhibit autologous B cell proliferation and antibody production through the production of NO and PGE2 and require cell-cell contact [141]. It is also reported that MDSCs can suppress B cell proliferation and antibody production through PGE2, iNOS, and arginase in both in vitro and in vivo [142]. Similarly, it is demonstrated that MDSCs suppress B cell expansion in mice through iNOS mechanism but not through arginase activity, PD-1-PD-L1 expression, and IL-10 production [143]. All of the above discussed studies were related to the effects of MDSCs on B cells in non-tumoral condition, and little is known regarding the effect of MDSCs on malignant B cells. In the majority of studies, it is suggested that MDSCs do not play an important role in the initial transformation of B cells to malignant lymphocytes. Moreover, it seems that these are malignant B cells which

provide a stimulatory condition for induction and expansion of MDSCs. Subsequently, activated MDSCs help to overexpansion of malignant cells. Thus, it seems that malignant B cells help to the development of MDSCs, and in turn, MDSCs support upregulation of malignant B cells. Several issues should be investigated regarding the stimulatory effects of MDSCs on B cell transformation and tumorigenesis process. For example, there is no comprehensive data regarding the cell contact-dependent mechanisms which may provoke malignant B cell expansion. Moreover, MDSCs can secrete several cytokines, such as IL-10 which may play an important role in the upregulation of malignant B cells, which are not studied until now. It is generally stated that MDSCs provide an immunosuppressive microenvironment (for example, through induction of Treg cells) in which malignant B cells can freely expand; however, it is unknown whether MDSCs can also affect B cell malignancies through IgA class switching mechanism.

Conclusion

MDSCs promote expansion of malignant lymphocytes in B cell malignancies in part through suppression of anti-tumor responses. Unfortunately, we have no comprehensive and justified reports about the immunobiology of MDSCs, their subsets characteristics, and functions in different B cell malignancies, particularly leukemia. It seems that there is a reciprocal relation loop between malignant B cells and immature myeloid cells in which malignant B cells induce and recruit MDSCs and MDSCs secrete tumor-expanding factors (Fig. 2); however, little is known regarding the detail of this relation and this issue deserves further investigations. Identification of effector factors behind the this relation loop and targeting them in combination with other potent immunotherapeutic approaches may be considered as novel promising approach for treatment of B cell malignancies.

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Conflicts of interest None

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